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REMARKS

The Office Action of October 21, 2002 has been carefully considered.

Claims 22-34 and 40-41 have been rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-26 of US Patent No. 5,908,697.

The independent claims of this application have now been amended to clarify the invention, reciting that the inhibitor acts chemically to prevent degradation of the active. Thus, the claims of the present application require a combination of a vesicle of a defined type, an active agent subject to *chemical* degradation, and a *chemical stabilizer for the active agent*.

The cited reference discloses only the vesicles of the defined type and an active agent. There is no disclosure or suggestion of combining the active agent with a stabilizer for the active agent.

The Office Action alleges that the claims are not patentably distinct because the present generic surfactant (claim 25?) reads on the specific surfactant claimed by the reference. While this may be true, Applicants submit that it is not relevant to the question of obviousness over the claims of this reference.

Thus, the '697 patent claims multilamellar vesicles

formed of membranes comprising a non-ionic surfactant of the sucrose ester type. Such liposomes may contain a variety of pharmaceutical actives, as recited, for example, in claim 26.

However, in the claimed invention, the claimed surfactant is not a chemical stabilizer for the active.

Moreover, in the '697 patent, the claimed surfactant is not disclosed as being a chemical stabilizer for the active.

Thus, while in both the claimed invention and in the '697 patent the vesicles may include a surfactant, *only the invention recites the use of a chemical stabilizer for the active which is disposed within the vesicles. Such an additional chemical stabilizer is not disclosed, suggested or claimed in the '697 patent.*

Withdrawal of this rejection is requested.

Claims 22-34 and 40-41 have been rejected under the judicially created doctrine of obviousness-type double patenting over claim 12 of US Patent No. 6,277,404.

Claim 12 of the '404 patent is directed to a pharmaceutical agent having at least one active agent incorporated in multilamellar vesicles which contain at least one "cationic agent" to give the vesicles a positive charge, and to cause it to adhere to surfaces. There is no disclosure or suggestion to incorporate a stabilizer for the pharmaceutical agent in such vesicles, and withdrawal of this

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rejection is requested.

Claim 22-38, 32-34 and 40-41 have been rejected under 35 USC 102(b) over CA 2133421.

The Canadian patent is directed to the preparation of vesicles of the type presently claimed, and which incorporate a polymer to structurally stabilize the vesicles. Applicants have argued that the claimed invention is directed to incorporation of an agent which chemically stabilizes the vesicles, and the Office Action now responds that applicant has not shown that the component taught by the reference does not perform this function.

In fact, the Canadian patent discloses the preparation of vesicles by incorporation of a monomer in the homogenous lamellar phase, shearing, and then polymerizing the monomer. There is no disclosure or suggestion whatever that the polymer which is formed is a chemical agent to inhibit the degradation of an active incorporated in the vesicles.

Applicants moreover submit that there is also no disclosure in the Canadian patent of any particular combination in which the chemical degradation of an active is inhibited by an additional agent provided in the vesicle. No such specific example has been cited in the Office Action.

The Office Action states that "applicant has not shown that the component taught by the reference does not perform

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this function." This is not, however, the obligation of applicant, in the absence of a disclosure by the reference of a combination in which the component arguably does perform this function. As the Office Action cites no specific example of a composition which allegedly falls within the invention, and the reference does not specifically teach the claimed invention, Applicants submit that the Office Action has met the burden of showing anticipation of the claimed invention, and withdrawal of this rejection is requested.

Claims 22-31, 33-34 and 40-41 have been rejected under 35 USC 102(b) over WO 96/31194.

Applicants previously argued that the vesicles of the invention differ from the classical multilamellar vesicles disclosed by the reference. This argument is rejected in the Office Action, which suggests amending the claims so as not to read on prior art vesicles.

While Applicants believe that the invention as it has been claimed clearly distinguishes over classical liposomes, the claims have now been further amended to clarify the difference, reciting that the *regular stack of concentric bi-layers extends from each vesicle core to periphery*. As has been shown clearly in the figures accompanying the Amendment filed on July 18, 2002, this is not the case in prior art vesicles in which the bilayers (see Figure 1) are neither

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regular nor concentric. In light of the agreement of the Examiner that the vesicles of this reference are prior art vesicles, and in light of the showing that the bilayers of prior art vesicles are not regular or concentric, and the specific admission of Applicants herein that only vesicles with regular, concentric bilayers fall within the invention, it is not clear what further language is necessary to distinguish the claimed vesicles from the prior art.

Withdrawal of this rejection is requested.

Claims 22-27 and 33-41 have been rejected under 35 USC 102(b) over Munechika et al.

Initially, it is noted that the liposomes of Munechika et al are classical liposomes and not the multilamellar vesicles of the invention. Reference is made to the discussion above with respect to WO 96/31194. For this reason alone, Munechika et al cannot anticipate the claimed invention.

Munechika et al discloses multilamellar liposomes containing lecithin, a surfactant and an drug which can be an enzyme. The vesicles may further contain "stabilizers" as disclosed at col. 3, lines 5-17, such stearylamine, cholesterol and polysaccharides.

Munichika et al, as disclosed in column 1, lines 49-61, is directed to a specific process for preparing a liposome composition, with inhibition of decomposition of the active

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agent during the process of forming the liposomes. Thus, according to Munechika et al, it is the process which is used to prevent degradation of the active agent during the preparation of the liposome; there is no disclosure of inhibiting degradation of the active after formation of the resulting liposome. This is clearly stated in column 1, lines 38 et seq. which refers to Japanese Patent 4-234820, and notes that preparation under low temperature conditions is desirable because most physiologically active peptides are labile against heat. In view of this, it is clear that the purpose of Munechika et al is to provide a method of preparing liposomes in which a heating step is avoided, thus preserving the integrity of the active principle during the manufacturing process.

Furthermore, it appears from column 2, lines 60 et seq. that tocopherol is used to stabilize the *lipid,* and not the active agent, and from column 3, lines 5 to 11, that the addition of the stabilizing agent is intended to reinforce the structure of the liposomes and not to inhibit any degradation of the active agent. None of the additives which are cited (polymers, cholesterol, fatty acids, stearylamin, albumin, gelatin and dextran) are known as examples of products used to inhibit oxidation of a chemical compound; these products do not have reducing properties or act as free-radicals

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scavengers.

Thus, there is no teaching in Munechika et al of the claimed invention, and withdrawal of this rejection is requested.

Claims 22-41 have been rejected under 35 USC 103 over CA 2133421 or WO 95/18601 in view of Munichika et al.

The Office Action admits that the primary references do not disclose addition of a stabilizer for a drug or enzyme, and cites Munichika et al for its teaching of liposomes containing lecithin, a surfactant, enzymes, stearylamine, cholesterol and an antioxidant, as well as other stabilizers such as gelatin, dextran and albumin.

Applicants submit, however, that Munichika et al does not cure the defects of the primary references. As discussed above, cholesterol, stearylamine, gelatin, dextran and albumin are not *chemical* stabilizers, they are only *physical* stabilizers, intended to stabilize the structure of the liposome. The only chemical stabilizer disclosed is tocopherol, which is specifically disclosed as stabilizing the lipid; there is no disclosure or suggestion of stabilizing the drug which is contained in the liposome, and no disclosure or suggestion that this drug needs to be stabilized. Munichika et al discloses that such materials might need to be stabilized during formation of the liposomes, but chooses to

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do so by reducing the temperature of formation. After formation, Munichika et al does nothing to stabilize the drug within the liposome. It is thus not clear why one would even look to Munichika et al for that purpose, since the only solution proposed by Munichika et al for that purpose is to maintain a low temperature. Munichika et al does not disclose adding any material at all to liposomes for the purpose of stabilizing the drug contained therein.

Withdrawal of this rejection is requested.

A patent to DeRosier has been cited as of interest to show that glycerol, albumin and sugars were known as enzyme stabilizers. This assertion is not completely correct since the teaching of DeRosier is, as it appears from column 3, lines 14 to 22, that it is necessary to combine a polysaccharide with a protein (albumin) to obtain a stabilizing effect on the enzymes of interest; each of the compounds, taken alone, does not have a stabilizing effect. This is confirmed by the passage at column 9, lines 27-32, where it clearly appears that the stabilizing agent is a mixture comprising albumin and different sugars.

In view of the foregoing amendments and remarks, Applicants submit that this application is now in condition for allowance. An early allowance of the application with amended claims is earnestly solicited.

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Respectfully submitted,

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APPENDIX

IN THE CLAIMS:

22. (Amended) A composition for stabilization of an active agent, comprising:

a plurality of multilamellar vesicles in the form of a regular stack of concentric bi-layers comprising at least one surfactant, said regular stack of concentric bi-layers extending from each vesicle core to periphery, and being separated by an interstitial liquid;

a first compound comprising said active agent encapsulated within said vesicles, said active agent being subject to chemical degradation; and

a second compound encapsulated within said vesicles, said second compound being an inhibitor of the chemical degradation of said active agent, said inhibitor acting chemically to prevent the chemical degradation, and being present within said vesicles in an amount sufficient to inhibit degradation of said active agent.

33. (Amended) A method for improving the stability of an encapsulated active agent which is subject to chemical degradation, comprising the steps of:

preparing a liquid crystal lamellar phase comprising at least one surfactant, at least one active agent subject to chemical degradation and at least one inhibitor of said

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chemical degradation which acts chemically to prevent said chemical degradation; and

subjecting said liquid crystal lamellar phase to shear, to obtain thereby a plurality of multilamellar vesicles in the form of a regular stack of concentric bi-layers comprising at least one surfactant, said regular stack of concentric bi-layers extending from each vesicle core to periphery, and being separated by an interstitial liquid, said vesicles containing therein said active agent and said inhibitor.

35. (Amended) A stabilized enzyme composition, comprising:

a plurality of multilamellar vesicles in the form of a regular stack of concentric bi-layers comprising at least one surfactant, said regular stack of concentric bi-layers extending from each vesicle core to periphery, and being separated by an interstitial liquid;

at least one enzyme encapsulated within said vesicles which is subject to degradation by chemical reaction; and

an inhibitor of the degradation by chemical reaction of said at least one enzyme present within said vesicles in an amount sufficient to inhibit degradation of said at least one enzyme,

said vesicles being obtained by preparing a preparing a liquid crystal lamellar phase comprising at least one

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surfactant, at least one active agent subject to chemical degradation and at least one inhibitor of said chemical degradation; and

subjecting said liquid crystal lamellar phase to shear to obtain said vesicles containing said active agent and said inhibitor therein.

36. (Amended) The composition according to claim 35, wherein said agent for [avoiding] inhibiting degradation of said enzyme is a known stabilizing agent for stabilizing proteins.

40. (Amended) A composition for stabilization of an active agent, comprising:

a plurality of multilamellar vesicles in the form of a regular stack of concentric bi-layers comprising at least one surfactant, said regular stack of concentric bi-layers extending from each vesicle core to periphery, and being separated by an interstitial liquid;

a first compound comprising said active agent encapsulated within said vesicles, said active agent being subject to chemical degradation; and

a second compound encapsulated within said vesicles, said second compound being an inhibitor of the chemical degradation of said active agent which acts chemically to prevent said chemical degradation, and being present within said vesicles

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in an amount sufficient to inhibit degradation of said active agent.

41. (Amended) A method for improving the efficacy of a stabilizing agent for an active agent, comprising the steps of:

preparing a liquid crystal lamellar phase comprising at least one surfactant, at least one active agent subject to chemical degradation and at least one inhibitor of said chemical degradation which acts chemically to prevent said chemical degradation; and

subjecting said liquid crystal lamellar phase to shear, to obtain thereby a plurality of multilamellar vesicles in the form of a regular stack of concentric bi-layers comprising at least one surfactant, said bi-layers extending from each vesicle core to periphery, and being separated by an interstitial liquid, said vesicles containing therein said active agent and said inhibitor.

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